SNMMI Value Initiative
SOCIETY OF NUCLEAR MEDICINE & MOLECULAR IMAGING

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submitted electronically via cms.gov

Dear Ms. Jensen:

Thank you for the opportunity to comment on the national coverage analysis (NCA) for Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease (AD) (CAG-00460N) proposed decision published on January 11, 2022. The Society of Nuclear Medicine and Molecular Imaging (SNMMI) and its more than 15,000 members set the standard for the practice of nuclear medicine and molecular imaging by creating guidelines, sharing information through journals and meetings, and advocating on key issues that affect molecular imaging, therapy, research and practice.

We appreciate efforts by the Centers for Medicare & Medicaid Services (CMS) to engage with interested stakeholders on this important topic. We have met with the Coverage and Analysis Group (CAG) concerning this NCA twice, and we are now submitting written comments to provide CMS with our recommendations regarding Medicare coverage for amyloid PET for patients who may be candidates for anti-amyloid monoclonal antibody therapy as well as for its use in patients who receive the therapy.

In our first comment letter regarding this NCA, we emphasized the importance of a national coverage policy for amyloid PET tracers to improve health equity and access to monoclonal antibodies for the treatment class for AD. Beta amyloid PET is essential for identifying patients who have beta amyloid in their brains who may, therefore, benefit from antibody products that target beta amyloid. Further, it is useful for quickly identifying patients who won't benefit from this therapy and could suffer from toxic side effects without therapeutic benefit. The trials that led to Food and Drug Administration (FDA) approval of aducanumab, the only monoclonal antibody targeted at amyloid for the treatment of AD that is approved by the FDA, required PET confirmation of the presence of beta amyloid in the brain.[1] Currently, there are three FDA-

[1] EMERGE and EMERGE and ENGAGE Topline Results: Two Phase 3 Studies to Evaluate Aducanumab in Patients With Early Alzheimer's Disease (https://investors.biogen.com/static-files/ddd45672-9c7e-4c99-8a06-3b557697c06f). 2019.

approved radiopharmaceuticals for the identification of amyloid plaque in the brain: ^{18}F florbetapir, ^{18}F flutemetamol, and ^{18}F florbetaben.

Under the existing national coverage determination (NCD) 220.6.20, Medicare only covers amyloid PET in the context of an approved clinical study under the Coverage with Evidence Development (CED) policy. In the draft national coverage determination (NCD) on monoclonal antibodies, CMS proposes to provide the following coverage for amyloid PET:

> For any CMS approved trials, or trials supported by the NIH, that include a beta amyloid positron emission tomography (PET) scan as part of the protocol, it has been determined that these trials also meet the CED requirements included in the Beta Amyloid Positron Emission Tomography in Dementia and Neurodegenerative Disease NCD (220.6.20), and one beta amyloid PET scan will be covered per patient, if the patient did not previously receive a beta amyloid PET scan.

This proposal inappropriately limits access to the critical diagnostic information provided by amyloid PET scans and creates inefficiencies for study sponsors and patients. It may also increase the economic and emotional burdens on patients with mild cognitive impairment who must expend resources to enroll in a clinical trial before getting a PET scan only to often find out after enrollment that they are not eligible to receive monoclonal antibodies because there is no beta amyloid present in their brain. We describe these concerns in greater detail below and provide recommendations for improvements CMS should make in the final NCD.

CMS should cover an amyloid PET scan before a patient is considered eligible for a CMS-approved study

Under the draft NCD, amyloid PET will only be covered as part of the protocol for a study that meets the CED requirements for coverage of monoclonal antibodies. In other words, patients must be enrolled in a clinical trial for the PET scan to be covered. However, the information provided by the PET scan helps to determine whether the patient meets one of the two criteria required for inclusion in the study--specifically whether the patient has amyloid pathology consistent with AD. In order for study sponsors to obtain the information about whether the patient is a candidate for the therapy (and therefore is a candidate for the clinical trial), the patient must first be enrolled in the trial.

This requirement is illogical, highly inefficient, and will create significant burdens for both trial sponsors and patients. Enrolling patients in a clinical trial, including obtaining the necessary informed consent agreement, requires substantial time and resources. It also requires educating the patient about the trial, the potential benefits of the study therapy, and the associated risks. Going through those steps for patients who should not receive the therapy and cannot continue in the trial wastes sponsor and patient resources and may cause unnecessary emotional and economic harm to patients, who will be educated about a treatment option that is not available to them at a time when other therapeutic options are extremely limited. It may also increase out-of-pocket costs for patients in underserved areas who need to travel to distant locations to participate in clinical studies. Such patients could spend time and money to reach trial sites only to learn that they are not in fact eligible to participate in the study.

Amyloid PET can identify patients who will not benefit from aducanumab ahead of time and simplify the enrollment process for patients and trial sponsors. It will also improve care for patients without beta amyloid as the treating professionals and caregivers can focus on treatment modalities that are appropriate for those patients. CMS should not limit coverage to trial participants but should provide coverage of amyloid PET to determine whether a patient should be enrolled in the trial. This will require that CMS finalize coverage for one PET scan to all patients considered candidates for aducanumab. CMS could accomplish this by retiring the beta amyloid CED NCD or by establishing additional, non-CED coverage of beta amyloid PET as part of the monoclonal antibody NCD. For additional reasons discussed below, we recommend that CMS retire NCD 220.6.20.

CMS should not finalize a limit of one beta amyloid PET scan per lifetime

Patients who are potential candidates for monoclonal antibodies should have an amyloid PET scan immediately before determining whether they are a candidate for monoclonal antibody therapy and before entering a covered trial. Amyloid status observed in earlier scans may no longer reflect a patient's current beta amyloid status. Studies evaluating use of blood biomarkers to determine amyloid status have noted the progression of some patients from positive blood/negative PET to positive PET.[2] There is no evidence to suggest that a single amyloid PET scan per patient is appropriate or that an outdated scan can provide the diagnostic information needed to determine

[2] West T, Kirmess KM, Meyer MR, Holubasch MS, Knapik SS, Hu Y, Contois JH, Jackson EN, Harpstrite SE, Bateman RJ, Holtzman DM. A blood-based diagnostic test incorporating plasma Aβ42/40 ratio, ApoE proteotype, and age accurately identifies brain amyloid status: findings from a multi cohort validity analysis. Molecular neurodegeneration. 2021 Dec;16(1):1-2.

whether a patient is currently a candidate for therapy. Furthermore, SNMMI does not understand the scientific basis for limiting beta amyloid PET to one scan per lifetime. Not only can CNS beta-amyloid status change over time, as discussed below, ongoing clinical trials for monoclonal antibody therapies for AD have used the results of post-treatment beta amyloid PET to inform a decision to discontinue monoclonal antibody therapy.

CMS should require post-treatment beta amyloid PET to be performed as needed to document the removal of beta amyloid PET from the brain

In addition to scans to determine a patient's eligibility for therapy, CMS should require and cover post-treatment PET scans to determine whether beta amyloid has been removed. The Phase 2 Lilly trial for a monoclonal antibody under development (donanemab) required multiple post-treatment PET scans and participants were switched to the placebo if amyloid plaque levels fell below certain parameters.[3]

CMS should require trial sites to use beta amyloid PET pre- and post-treatment to assure accurate measurement of beta amyloid. CMS should allow as many PET scans as are needed to ensure that the trial design is optimal and reliable and provides physicians the information needed to make informed decisions about initiating and continuing therapy. Notably, one or more scans during therapy to verify removal of amyloid must be covered.

CMS should retire the current PET CED in conjunction with finalizing the monoclonal antibody NCD

We reiterate our previous requests that CMS retire NCD 220.6.20 as soon as possible. Continuation of limitations on amyloid PET while other uses of PET for AD, such as tau PET, are covered at the discretion of the Medicare Administrative Contractors (MAC) creates an illogical and confusing situation for physicians, patients, and clinical trial designers. Under the current disjointed coverage, patients can, in principle, have an unlimited number of tau PET scans, but can have only one amyloid PET scan - and that single PET scan is limited to CED. Under current coverage, there is an incentive to preferentially use tau PET to identify patients for clinical trials and for diagnosing AD even though this is not the current standard of care. Coverage of tau and

[3] Mintun, MA et al. Donanemab in Early Alzheimer's Disease. New England Journal of Medicine. 2021 May 6; 384: 1691-1704.

beta-amyloid PET should be equivalent, i.e. at the level of care currently allowed for tau PET, to allow full access to appropriate diagnostic tools.

We understand that CMS may be awaiting results from the New IDEAS trial that is approved under the CED requirements for NCD 220.6.20 before acting on our request. The completed IDEAS trial found beta-amyloid PET was associated with changes in management in more than 60% of patients with mild cognitive impairment or dementia of uncertain etiology and a change in diagnosis in 36% of patients.[4] However, the data that will come from New IDEAS is not relevant to the proposed decision for monoclonal antibodies. The design and endpoints of New IDEAS are completely different than the proposed CED requirements in the draft NCD.

Furthermore, New IDEAS is currently undergoing a 6-month pause due to problems in enrolling underrepresented populations. The accrual phase for the study was originally projected to close in Q3 of September 2023. However, closure of accrual is based on the enrollment of 7,000 participants and closure is now expected in 2024. Therefore, while preliminary data from New IDEAS are very promising, we do not believe CMS should wait for additional evidence to retire the amyloid PET NCD. If anything, CAG should be more concerned with results of aim 2 of IDEAS, which are due imminently.[5]

CMS should resolve inconsistencies in coverage for diagnostic tools that may be used in CED trials for monoclonal antibodies by retiring NCD 220.6.20 and providing coverage of amyloid PET at MAC discretion.

CMS Should Not Limit Sites of Service for Approved Clinical Trials to Hospitals

In its proposed decision CAG stated, "We also propose that the setting for CMS-approved clinical trials remain in hospital-based outpatient facilities as this ensures integrated and coordinated care, availability of advanced imaging or other diagnostic tests, and rapidly-available advanced care if needed." There are many clinics and multispecialty groups who regularly participate in clinical trials and have the expertise to enroll patients and implement complex clinical trials. Additionally,

[4] Rabinovici GD, Gatsonis C, Apgar C, et al. Association of Amyloid Positron Emission Tomography With Subsequent Change in Clinical Management Among Medicare Beneficiaries With Mild Cognitive Impairment or Dementia. *JAMA.* 2019;321(13):1286–1294. doi:10.1001/jama.2019.2000

[5] Aim 2: Determine if amyloid PET is associated with a ≥10% reduction in 12-months CMS claims-derived hospital admissions and emergency department (ED) visits in study patients vs. controls. https://www.ideas-study.org/Original-Study

many academic faculty practice plans where patients with mild cognitive impairment are seen and treated are associated with hospitals but are not hospitals themselves are actually enrolled in Medicare as physician offices. Furthermore, requiring that patients who are potentially eligible for a CMS approved clinical trials travel to hospitals to get a PET scan is burdensome, especially for patients in underserved areas and may inhibit enrollment in those trials. We would like to note that in IDEAS about 69% of participants were referred to non-hospital-based PET facilities.[6] Limiting the trials to only hospitals would greatly impede patient access due to geographical and payment considerations and contribute to health care disparities.

Appropriate reimbursement of amyloid PET is necessary

Currently, the three amyloid PET tracers are reimbursed an average of nine percent of their pass-through payment rate due to being bundled in with the scan in the hospital outpatient prospective payment system (OPPS). Under the Medicare Physician Fee Schedule (MPFS), which includes non-hospital facilities, amyloid PET tracers are paid separately. The current bundling policy will make it impracticable for hospitals to participate in the therapy CED trial (for those patients that do not already have a PET scan).

New IDEAS illustrates the chilling effect that the lack of appropriate reimbursement of amyloid PET scans has on the enrollment of hospitals in this study. Only approximately 16 hospitals out of the 125 hospitals who participated in the IDEAS trial are participating in the New IDEAS trial. In fact, the 2020 Government Accountability Office (GAO) Report noted the impact of the current OPPS policy. In their report, the GAO acknowledged that hospitals' use of diagnostic radiopharmaceuticals was higher when drugs were eligible for the initial pass-through payments than when they were bundled with the scan. Additionally, at the CMS Advisory Panel on Hospital Outpatient Payment (HOP) meeting on August 31, 2020, the panel recommended that "CMS pay separately for all diagnostic radiopharmaceuticals."

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[6] *Supra* at note 4.

In conclusion, in conjunction with the final NCD on monoclonal antibodies directed against amyloid for the treatment of AD, we strongly recommend that CMS remove the coverage limitations on amyloid PET by:

- Retiring NCD 220.6.20;
- Establishing that amyloid PET will be covered (pre-clinical trial) to identify patients who are candidates to receive monoclonal antibody therapy and as necessary after therapy initiation to inform treatment decisions; and
- Clarifying that there is no lifetime limit on the number of medically necessary amyloid PET scans that a patient can receive.

SNMMI appreciates the opportunity to comment on CAG-00460N. As always, we are ready to discuss any of our comments or meet with CMS/CAG on the above issues. In this regard, please contact Julia Bellinger, Director of Health Policy and Regulatory Affairs at jbellinger@snmmi.org.

Respectfully Submitted,

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President, SNMMI